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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/470,168	12/22/1999	Mathew Grant Boston	GC538-2	5850

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT

PAPER NUMBER

1652

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Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/470,168

Applicant(s)

BOSTON ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 15,16,18,20-28,30-51,58-75 and 77-82 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 15,16,18,20-28,30-51,58-75,77-82 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_ 6) ☐ Other: \_\_\_\_\_

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## **DETAILED ACTION**

### ***Continued Prosecution Application***

The request filed on February 27, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/470,168 is acceptable and a CPA has been established. An action on the CPA follows.

The Preliminary amendment filed February 27, 2002 canceling claims 29 and 76 and amending claims 15, 18, 20, 25, 26, 31, 47-51, 63, 73 and 77-79 and adding claims 80-82 has been entered.

Claims 15, 16, 18, 20-28, 30-51, 58-75 and 77-82 are pending.

### ***Claim Objections***

Claims 37 and 69 are objected to because of the following informalities:

"Enterobacteriaceae" is mistyped. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 16, 18, 20-28, 30-51 and 58-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

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specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15 and 18 are directed to a method for the non-fermentative production of 2-KLG from a carbon source comprising oxidizing the carbon source and reducing the resulting oxidation product to 2-KLG wherein the carbon source is any 6-carbon sugars, etc. The dependent claims recite the specific environment and the mode of a process. Claim 15(a) recites "at least three oxidative steps" whereas claim 18 recites three oxidative steps. Therefore, the claims encompass pathways from any 6-carbon sugar or its derivative, both naturally occurring and modified, to KLG through any intermediate. The specification discloses oxidation of glucose to gluconate by glucose dehydrogenase and then gluconate by gluconate dehydrogenase and 2-KDG dehydrogenase to DKG. DKG is then reduced to 2-KLG. This pathway is known in the art. Therefore, said reactions are characterized only by the final product, 2-KLG. The specification fails to describe other representative reactions that produce 2-KLG from any carbon source. No oxidase or reductase using co-factors other than NADP/NADPH are described. Therefore, the claims are drawn to a method of use of a genus of molecules described by broad function comprising genera of various functionally and structurally different enzymes catalyzing various reactions and having different substrate specificity. Therefore, the scope of the claims includes numerous variants,

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and the genus is highly variant because a significant number of structural and functional differences between genus members is permitted. Given this lack of description of common structural attributes or characteristics that identify members of the genus of enzymes catalyzing the specific reaction, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 15, 16, 18, 20-28, 30-51 and 58-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing 2-KLG from glucose using glucose dehydrogenase, gluconate dehydrogenase, 2-KDG dehydrogenase and reductase A:F22Y/A272G while regenerating NADP(H), does not reasonably provide enablement for producing 2-KLG from any 6-carbon sugar or its derivative using any oxidase and reductase dependent on a co-factor other than NADP(H). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 15, 16, 18, 20-28, 30-51 and 58-62 are so broad as to encompass any combination of oxidase/reductase catalyzing unspecified reactions. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard

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to the extremely large number of potential enzymes broadly encompassed by the claims. However, in this case the disclosure is limited to producing 2-KLG from glucose using glucose dehydrogenase, gluconate dehydrogenase, 2-KDG dehydrogenase and reductase A:F22Y/A272G.

The general pathway for producing 2-KLG from glucose disclosed in the specification is known in the art. The specification provides no guidance as to what are other oxidation/reduction reactions that can produce 2-KLG from any 6-carbon sugar.

The specification does not support the broad scope of the claims which encompass all oxidases and reductases because it is known in the art that enzymes are highly substrate and cofactor specific. As discussed above, the specification teaches only one pathway leading from glucose to 2-KLG using NADP(H) dependent dehydrogenases and reductase. There is no teaching of dehydrogenases/reductases using cofactors other than NADP/NADPH. It is also known in the art that enzymes are highly sensitive to reaction conditions such as salt composition and concentration. While the composition of salts recited in claim 61 is suitable for use with reductase A:F22Y/A272G, it is not necessarily applicable for other enzymes (page 26). The specification provides insufficient guidance as to which of the essentially infinite possible choices of combinations of enzymes, cofactors and conditions is likely to be successful.

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Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any 6-carbon sugar or derivative thereof as a starting material from which any number of oxidases and reductases using cofactors different than NADP/NADPH produce 2-KLG. Without sufficient guidance, determination of enzymes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.  
Claims 15, 16, 18, 20-28, 30-51, 58-75 and 77-82 and are rejected under 35

U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15, 18 and 80 are drawn to a process comprising steps in any order further reciting first product, second product, etc. "In any order" is confusing because it contradicts the numbered sequence of the steps/products. Further, it is confusing because if the sequence of the steps is reversed, for example, it would be impossible to arrive at 2-KLG.

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Claims 15 and 18 recite carbon source "selected from the group consisting of 6-carbon sugars, mixture of 6-carbon sugars, and 6-carbon sugar acids, and is capable of being converted to an ascorbic acid (ASA) intermediate". The metes and bounds of 6-carbon sugars, etc. is given by non-limiting examples rendering the scope of the claims unascertainable (page 7, lines 18-27). Further, the scope of "intermediate" is unclear rendering the metes and bounds of the claims indefinite. The recitation of "capable of" refers to a latent ability which may or may not be expressed for the function of the invention. Being "capable of" is not equivalent of actually doing so.

Claim 16 is indefinite because the term "KDG" is not defined in the specification.

Claim 30-32 are incomplete as dependent from canceled claim 29.

Claim 41 is indefinite because it encompasses a mutation in any dehydrogenase naturally-occurring in a given host cell, not necessarily GDH, that may act in processes other than the production of 2-KLG. The specification does not define which dehydrogenases other than GDH are included in the scope of the claim rendering the metes and bounds thereof unclear.

Claims 60 and 62 recite salt and its concentration, respectively. Since "salt" encompasses an infinite number of compounds, the claims are indefinite because they do not distinctly claim salt(s) having said concentration. Also, in claim 62 "at" appears to be omitted after "salt".



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With regard to claim 61, some salts are recited twice: as a word and by a formula. A second comma on the 3rd line is not needed.

Claims not specifically discussed herein are rejected as dependent on the rejected base claim.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 16, 18, 20, 24, 26, 27, 45 and 80-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Kulbe et al.

Kulbe et al. teach process for the intrasequential cofactor regeneration in enzymatic synthesis with one or plurality of steps. In this process, a substrate is oxidized by enzymes and oxidation product thus obtained is transformed by enzymes into a reduction product. The desired final product is isolated by known processes, and two enzymes presenting the same specificity as to cofactor are used for the associated oxidation and reduction processes (abstract, Figures 4, 7 and 8). They teach that this process is particularly well adapted for the production of vitamin C, intermediate products thereof or precursors thereof and illustrate the production of 2-KLG from D-

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gluconic acid using three oxidative and one reductive steps wherein NADP and NADPH are recycled (abstract, Figure 8, for example).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 15, 16, 18, 20-28, 30-51, 58-75 and 77-82 are rejected under 35

U.S.C. 103(a) as being unpatentable over Light et al. in view of Kulbe et al.

Light et al. (US Patent 4,758,514) teach the pathway glucose - 2-KLG (column 1, lines 16-29). They further teach the production of 2-KLG from glucose by *Erwinia* cell transformed with 2,5-DKG reductase gene (column 17, line 62 through column 20, line 5, Examples 5 and 6). This process comprises enzymatic oxidation of glucose by *Erwinia* into DKG and enzymatic reduction of DKG to 2-KLG. Since enzymes involved in oxidation of glucose to DKG are known in the art, it would have been obvious to the one of ordinary skill in the art at the time the invention was made to carry out non-fermentative oxidation of glucose into DKG using purified enzymes or cells transformed with a DNA encoding an enzyme. One would have been motivated to use non-fermentative oxidation of glucose into DKG because it allows a more efficient and

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convenient production of larger quantities of DKG and KDG compared with the fermentative production. In particular, host cells of the family Enterobacteriaceae are suitable because the methodology is greatly advanced as applied to said cells.

Furthermore, they are also known to produce the requisite enzymes.

The teachings of Kulbe et al. are outlined above. They further teach sources of various enzymes. They teach that this process can be operated continuously, uses inexpensive substrates which are completely converted and provides high yields of very pure products. It is less polluting and cheaper. Therefore, Kulbe et al. provide the motivation and the expectation of success. It would have been obvious to the one of ordinary skill in the art at the time the invention was made to employ known oxidative and reductive enzymes to produce 2-KLG and at the same time to recycle the cofactor choosing oxidases and reductases using oxidized and reduced forms of the same cofactor. As a matter of choice the process can be continuous or batch employing soluble or immobilized enzymes or cells/membranes producing the requisite enzymes.

Claims 15, 16, 18, 20-28, 30-51, 58-75 and 77-82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powers et al. in view of Kulbe et al.

Powers et al. (US Patent 5,795,761) teach the pathway glucose - 2-KLG. They further teach that a number of microorganisms such as *Erwinia*, *Acetobacter* and *Gluconobacter* can produce 2,5-DKG from glucose and the second group can reduce

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2,5-DKG to 2-KLG (column 1, lines 25-61). They teach reductase A:F22Y/A272G mutant (Figure 10, for example) catalyzing conversion of 2,5-DKG to 2-KLG. Since enzymes involved in oxidation of glucose to DKG are known in the art it would have been obvious to the one of ordinary skill in the art at the time the invention was made to carry out non-fermentative oxidation of glucose into DKG using purified enzymes or cells transformed with a DNA encoding an enzyme. One would have been motivated to use non-fermentative oxidation of glucose into DKG because it allows a more efficient and convenient production of larger quantities of DKG and KDG compared with the fermentative production. In particular, host cells of the family Enterobacteriaceae are suitable because the methodology is greatly advanced as applied to said cells. Furthermore, they are also known to produce the requisite enzymes.

The teachings of Kulbe et al. are outlined above. They further teach sources of various enzymes. They teach that this process can be operated continuously, uses inexpensive substrates which are completely converted and provides high yields of very pure products. It is less polluting and cheaper. Therefore, Kulbe et al. provide the motivation and the expectation of success. It would have been obvious to the one of ordinary skill in the art at the time the invention was made to employ known oxidative and reductive enzymes to produce 2-KLG and at the same time to recycle the cofactor choosing oxidases and reductases using oxidized and reduced forms of the same co-

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factor. As a matter of choice the process can be continuous or batch employing soluble or immobilized enzymes or cells/membranes producing the requisite enzymes.

Claims 37, 39-41, 69, 70 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Light et al. in view of Kulbe et al. and further in view of Cha et al.

As discussed above, host cells of the family Enterobacteriaceae are particularly suitable for carrying out the claimed processes and it would have been obvious to use them. The following rejection makes it more specific.

The teachings of Light et al. and Kulbe et al. are outlined above. Cha et al. isolated a *Pantoea citrea* gene encoding glucose dehydrogenase. The teach inactive mutants of said gene (page 72, Table 2).

It would have been obvious to the one of ordinary skill in the art at the time the invention was made to use as a host cell a *Pantoea citrea* cell because of its convenience in view of the specific teachings of Cha et al.

Claims 37, 39-41, 69, 70 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Powers et al. in view of Kulbe et al. and further in view of Cha et al.

As discussed above, host cells of the family Enterobacteriaceae are particularly suitable for carrying out the claimed processes and it would have been obvious to use them. The following rejection makes it more specific.

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### ***Response to Arguments***

Applicant's arguments filed February 27, 2002 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph, (written description), "Applicants submit [that] a description of structural attributes for every enzyme that could be used in the claimed process is required. Members of the genus may be defined by their function" (paragraph bridging pages 7 and 8). It is agreed that a description of structural attributes for every enzyme that could be used in the claimed process is not required. However, the function alone given the fact that several various genera of enzymes with different function s would fall within the scope of the claims is insufficient. Applicants did not provide the correlation between the function and structural attributes or any other identifying characteristics (including cofactor).

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With regard to the 112, 1st paragraph, (enablement), Applicants argue that claim 63, 73 and 80 specifically recite the carbon source as glucose and specifically recite glucose dehydrogenase as the oxidative enzyme. The examiner agrees with that and notes that these claims are not included in the rejection.

With regard to the 103(a) rejection, Applicants argue that a recycling of the co-factor is a crucial element of the instant invention (pages 9 and 10). However, absent showing of unexpected results the regeneration of NADP(H) is obvious when known enzymes are used in the production of 2-KLG from glucose. The instant claims are not drawn to a non-obvious invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

  
Elizabeth Slobodyansky, PhD  
Primary Examiner

April 25, 2002